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UNITED STATES DISTRICT COURT
for the
DISTRICT OF NEW JERSEY

CHAYA GROSSBAUM and MENACHEM GROSSBAUM, her spouse, individually and as *guardians ad litem* of the infant ROSIE GROSSBAUM, Plaintiffs, vs. GENESIS GENETICS INSTITUTE, LLC, of the State of Michigan, MARK R. HUGHES, NEW YORK UNIVERSITY SCHOOL OF MEDICINE and NEW YORK UNIVERSITY HOSPITALS CENTER, both corporations in the State of NEW YORK, ABC CORPS. 1-10, JOHN DOES 1-10, Defendants.	CIVIL ACTION NO. 07-CV-1359 (GEB)

PLAINTIFFS' SUPPLEMENTAL STATEMENT OF UNDISPUTED MATERIAL FACTS AS TO BOTH DEFENDANTS' STATEMENT OF UNDISPUTED MATERIAL FACTS

BACKGROUND INFORMATION

1. This case involves the application of two scientific developments, in-vitro fertilization and preimplantation

genetic diagnosis—the opportunity to study the genetic make-up of an embryo (a fertilized egg) to determine the presence of genetic disorders prior to implantation in the mother's womb to create pregnancy and ultimately, the birth of a health child. Facts surrounding in-vitro fertilization well recognized in public discourse and preimplantation genetic diagnosis were described in the year 2000 in the textbook entitled "An Illustrated Textbook and Reference for Clinicians; An Atlas of Preimplantation Genetic Diagnosis" at Page 11:

> Preimplantation genetic diagnosis (PGD) is a principally new approach for the prevention of genetic disorders, which avoids the need for prenatal diagnosis and termination of pregnancy. It is based on control of the processes of oocyte maturation, fertilization and implantation, to select and transfer back to the uterus only normal embryos, and achieve an unaffected pregnancy and the birth of a health baby. In this way, couple at high risk of having offspring with genetic disease will have an option to control the outcome of their pregnancy from the very outset. Although this option involves ovarian hyperstimulation and *in vitro* fertilization (IVF), available experience shows that PGD appears to be an acceptable procedure in many ethnic groups all over the world.

(Pl. Exh. 1.)

2. The foundation for understanding the process described above involves an introduction to genetics. From Wikipedia, the free encyclopedia, an "Introduction to Genetics," is attached as Pl. Exh. 2.

3. The following is a glossary of terms required for the factual understanding of the issues in this case:

   a. Allele is "one member of a pair [as defined for the purpose of this case taken from Wikipedia] of different forms of a gene." In this case, the mutation for the mother was found at a place described as Exon 11 at G542X. The husband's mutation was located on Exon 10 at DeltaF508.

b. Heterozygous: "if two alleles are different at one locus, the person is heterozygous at that genetic location." [dna.gov → Glossary]

c. Heterozygosity: "the human genome contains two copies of each gene: a paternal and a maternal allele. A mutation affecting only one allele is called heterozygous. When both alleles of a gene harbor mutations, the mutations are difference. The mutations are called compound heterozygous." [Medicinenet.com]

d. PCR is a polymerase chain reaction. "The polymerase chain reaction is a scientific technique in molecular biology to amplify a single or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. Developed in 1983 by Kary Mullis, PCR is now a common and often indispensable technique used in medical and biological research labs for a variety of applications. These include DNA cloning for sequencing, DNA-based phylogeny, or functional analysis of genes; the diagnosis of hereditary diseases; the identification of genetic fingerprints (used in forensic sciences and paternity testing); and the detection and diagnosis of infections diseases. In 1993, Mullis was awarded the Nobel Prize in Chemistry for his work on PCR." [Wikipedia] Also, a "process used in DNA identification testing in which one or more specific small regions of DNA are copied using a DNA polymerase enzyme so that a sufficient amount of DNA is generated for analysis." [NFSTC Science Serving Justice]

e. Allele Dropout: "failure to detect an allele within a sample or failure to amplify an allele during PCR." [dna.gov → Glossary]

f. Multiplex: a "system for analyzing several loci at once." [dna.gov → Glossary]

g. Linkage Analysis is another name for multiplex PCR. Linkage is the tendency for genes and other genetic markers to be inherited together because of their location near one another on the same chromosome. Because DNA segments that lie near each other on a

chromosome tend to be inherited together, markers are often used as tools for tracking the inheritance pattern of a gene that has not yet been identified, but whose approximate location is known.

h. Mutation: changes in DNA caused by mutation can cause errors in protein sequence, creating partially or completely non-functional proteins. To function correctly each cell depends on thousands of proteins to function in the right place at the right time. When a mutation alters a protein that plays a critical role in the body, a medical condition can result. A condition caused by mutations in one or more genes is called a genetic disorder. [Wikipedia]

i. Blastomere: "a type of cell produced by division of the egg after fertilization." [Wikipedia] In this case, the blastomere was the name given to the cell extracted from the embryo during in-vitro fertilization and sent to Genesis Genetics for laboratory analysis as to the presence of the cystic fibrosis gene mutation in the strand of DNA contributed from the mother and the father.

j. Cystic Fibrosis: as noted in the decision in 1981 of Schroeder v. Perkel, 87 N.J. 53 (1981) at Pg. 58:

> Cystic fibrosis is one of the most common fatal genetic diseases in the United States and affects approximately 1 out of every 1,800 babies. An insidious and incurable disease, cystic fibrosis is carried by some parents as a recessive gene.
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> ***
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> In general, cystic fibrosis causes certain glands to malfunction and produce abnormally thick mucous. The most commonly affected body systems are the digestive tract and the respiratory system. In the digestive tract, mucous blocks ducts in the pancreas, preventing enzymes from reaching the intestines. One result is an inability to digest fats. Respiratory problems,

however, are the most serious symptoms of cystic fibrosis. In the respiratory system, mucous clogs passages and causes air to become trapped in the lungs. Respiratory problems cause chronic pulmonary infection, emphysema and over 90% of all deaths of patients with cystic fibrosis. Metabolic Basis of Inherited Disease 1684 (4th Ed. 1978).

k. Wrongful Life/Wrongful Birth: the distinction between these two very similar causes of action relates to the ability of the mother to have terminated the pregnancy upon being informed at the appropriate time of the disability of her fetus. See Procanik by Procanik v. Cillo, 97 N.J. 339, 347-348 (1984).

THE PLAINTIFFS COME TO
PREIMPLANTATION GENETIC TESTING

4. Plaintiffs chose to undertake IVF and PGD to reduce their 25 percent chance of having an affected child. (Declaration of Chaya Grossbaum; Pl. Exh. 3.)

5. The medical community recognized that "Couples whose children are at increased risk for a specific genetic disorder can benefit from PGD.… PGD is an alternative to prenatal tests such as amniocentesis or chorionic villus sampling and since it is performed before a pregnancy has begun, it may be more acceptable to couples who … have objections to termination of pregnancy." (See "Review: Molecular Diagnostics in Preimplantation Genetic Diagnosis" out of the Mayo Clinic, Department of Laboratory Medicine and Pathology, published in Journal of Molecular Diagnostics, No. 4, No. 1, February 2002 at Page 11; learned treatise produced by the Plaintiffs to the Defendants in discovery; Pl. Exh. 4.)

6. PGD was well recognized in Europe in the publications of the European Society of Human Reproduction and Embryology. The doctors at the Department of Molecular Cell Biology and Genetics, and the Department of Obstetrics and Gynecology at Academic Hospital, Maastricht, The Netherlands, published first at the Annual Meeting of the European Society of Human Reproduction and Embryology in June 1999

at Tours, France, and later in the journal, Molecular Human Reproduction, Vol. 6, No. 5, Pages 391-396, in the year 2000, that "for couples at risk of transferring a genetic disorder to their offspring, PGD offers an alternative to prenatal diagnosis. By choosing PGD, the difficult decision of pregnancy termination after genetic diagnosis by chorionic villus sampling or amniocentesis in the first and second trimesters of gestation can be avoided." (Pl. Exh. 5 at Page 391.)

THE PLAINTIFFS' NEW JERSEY CONNECTION

7. As stated in the Declaration of Chaya Grossbaum at Pl. Exh. 3:

a. I have been a New Jersey resident all of my life with the exception of three years after my marriage in August, 2002 when my husband and I temporarily lived in Brooklyn, New York prior to our childbearing years. It was always our intention to move back to New Jersey when we began a family.

b. I was born in Morristown, New Jersey and went to the Morristown schools, except for the last two years of high school, when I went away to school. I met my husband when I was in high school in Morristown, New Jersey, and he was a student at the Rabbinical College of America, also in Morristown, New Jersey.

c. My parents have been New Jersey residents since before I was born. My husband was born and raised in Minnesota.

d. Our family plan was that when I had our first baby we would return to New Jersey. In pursuit of that plan: (a) I came under the care of Marla Scott, CNM and Judy Caruso, CNM at Midwives of Denville, Boonton, NJ; (b) delivered the baby, Rosie, at Saint Clare's Hospital-Denville Campus, Denville, New Jersey; (c) prior to the baby's birth, arranged for a pediatrician, Dr. Richard Dicker, whose practice was located at 10 Broadway in Denville, New Jersey.

e. In addition, when I was informed, two weeks after Rosie was born, that she was a cystic fibrosis baby, I arranged for consultation with the Cystic Fibrosis Center at Morristown Memorial Hospital, Morristown,

New Jersey, where Rosie has been a patient since her birth approximately six years ago.

f. The only reason for having contact with NYU Medical Center and its Fertility Clinic was the IVF services offered by that institution allowed a rabbi to oversee the IVF processes to confirm compliance with Jewish law.

8. When the Plaintiffs began the process of IVF/PGD, it was known that they were both carriers of the cystic fibrosis gene mutation, which was characterized as compound heterozygous. (Genesis Exh. 13 at CG018, CG019, CG021.)

9. The significance of compound heterozygous mutations was well described in the medical literature, and particularly in the aforementioned Mayo Clinic article by Dr. Alan R. Thornhill, the paper stated:

> …for compound heterozygous…conditions, the consequences of ADO [allele dropout] can be catastrophic, as misdiagnosis and subsequent transfer of affected embryos can occur. Indeed ADO is the most likely cause of reported errors in PGD of cystic fibrosis in which affected compound heterozygote embryos were misdiagnosed as carrier embryos because the analysis used could only detect one of the inherited mutations.

(Pl. Exh. 4 at Page 14.)

10. Also from the aforementioned publication:

> In addition to reducing ADO, strategies have been proposed to increase the detection of ADO. One such strategy is the use of linked markers which simultaneously controls for contamination. Use of one or two liked markers reduces undetected ADO by approximately 50% and 75% respectively and with three linked markers ADO is virtually always detected. The use of linked markers carries considerable advantages not only from the point of view of reducing the possibility of misdiagnosis, but also by potentially increasing the number of embryos available for transfer.

(Pl. Exh. 4 at Page 16.)

11. Genesis Genetics and Dr. Hughes did not use linkage analysis in analyzing the cells from embryos sent by NYU on behalf of the Plaintiffs. Notwithstanding what Dr. Hughes said in his declaration submitted as Exhibit 6 by the Defendants Genesis Genetics and Hughes, in his first deposition on February 19, 2009, Dr. Hughes admitted that Genesis Genetics had the technology to perform linkage analysis, but did not do so. Dr. Hughes was specifically asked in his deposition:

> Q. Were you aware that that type of testing was done at other laboratories in the United States?
>
> A. We were all trying to do it, which was why I wanted to have those embryos, so we can set genetic phase for the family, and do that. …in order to look at polymorphic markers you need to have some way to link the marker to the mutation. …we had the equipment to do it, but we needed to have another sample, so you need a member of the family. If this couple had a healthy child or if this couple had an affected child or a sister or a brother that were carriers that we could get a sample from, the idea would be then, to look at those markers and set what's called "genetic phase" to determine whether the marker - which markers are linked to the mutation.

(Hughes Dep. 2/19/09 T:57-8 to 57-25; Pl. Exh. 6.)

12. After stating that he needed more information about the Grossbaums, he stated:

> If they had to go through this another time, we would then try to develop a better test using those genomic markers.

(Hughes Dep. 2/19/09 T:58-12 to 58-14; Pl. Exh. 6.)

13. Dr. Hughes also admitted that he was "perfectly aware of all of that technology." (Hughes Dep. 2/19/09 T:58-21 to 58-22; Pl. Exh. 6.)

14. Dr. Hughes agreed that "if the cause of the misdiagnosis was allele dropout, if that was the cause of the problem, and if we had a sample that they would give us that would allow us to use the technology, absolutely, it would have helped, and we do that routinely now." (Hughes Dep. 2/19/09 T:59-21 to 59-25; Pl. Exh. 6.)

15. Dr. Hughes further claimed that he asked for the required samples of the Grossbaums in order to do linkage analysis, but claimed "they didn't want to give them to us, but I can't be sure." (Hughes Dep. 2/19/09 T:60-22 to 60-23; Pl. Exh. 6.)

16. Plaintiff, Chaya Grossbaum, declared that neither Dr. Hughes nor anyone else asked them to supply blood samples from other members of the family which would have satisfied Dr. Hughes' need to do the linkage analysis. (Declaration of Chaya Grossbaum; Pl. Exh. 3.)

17. Dr. Charles R. Strom, Plaintiffs' consultant expert on laboratory tests for cystic fibrosis in PGD, and the author of such papers as "Genetics: Reliability of Polymerase Chain Reaction (PCR) Analysis of Single Cells for Preimplantation Genetic Diagnosis," published in the Journal of Assisted Reproduction and Genetics, Vol. 11 No. 2, **1994** [emphasis supplied], stated at depositions:

> …The concept of multiplex PCR for the detection of allele dropout was well established by the year 2000 when [he] left RGI [Reproduction Genetic Institute of Chicago]. Other people began instituting them in their own programs at that point and the Thornhill report was what he had implemented.

(Strom Dep. 5/4/10 T:38-22 to 39-5; Pl. Exh. 7.)

18. The laboratory records of the analysis of the Plaintiffs' embryos on the page labeled "DNA Sequencing – Genotyping Assay" in the handwriting of Dr. Mark Hughes came the statement, "always concerned for ADO (we should try to obtain untransfered embryos for next time assay)." This latter comment allows for only one factual conclusion: there was an issue as to the suitability as to the embryos for implantation from the DNA studies by Genesis Genetics;

there was the potential for needing another group of embryos at a later time; there were techniques to improve the reliability of the studies in the next submission of embryos from the Plaintiffs by using "linkage analysis." (Pl. Exh. 8.)

19. The Genesis Genetics records contained a page labeled "Message" (Pl. Exh. 9) addressed to "NYU IVF Team" that contained the statement, "We are disappointed with the results given the large number of amplification failures for one of the two CFTR alleles…If the couple chooses a transfer with this partial data set, those samples displaying the G allele at G542X would be predicted unaffected, assuming no allele dropout. However, ADO is possible in compound heterozygote testing such as this, and even more likely given the embryo quality." The memo went on to emphasize the need for prenatal testing and contemplated the potential for the Plaintiffs rejecting further IVF procedures because of the poor quality of the laboratory studies up until then.

20. In Genesis Genetics Institute's final report (Pl. Exh. 10) at Page 2: there is a clear indication that the outcome of the analysis was "disappointing." The gene location for the mutation on the chromosome was studied under testing that "has been routinely performed since 1991." The reasons for the "disappointing" outcome were elaborated upon. Allele dropout was emphasized as "a distinct concern in this sample set." The concern for allele dropout "could result in a misdiagnosis." The laboratory was relying on the informed consent of the Plaintiffs to exonerate any responsibility it would have for implantation of a "disappointing" study. Dr. Hughes further advised NYU of the statistical risk of misdiagnosis in the general population—a further indication that the studies could present a real danger of a misdiagnosis.

21. Dr. Hughes in his expert deposition of May 14, 2010 claimed that the documents referred to in No. 19 and No. 20 above (Pl. Exh. 9 and Pl. Exh. 10) were his actual final report to NYU. (Hughes Dep. 5/14/10 T: 66-3 to 66-7; Pl. Exh. 11.)

Comment: notwithstanding that the documents referred to in Pl. Exh. 9 and Pl. Exh. 10 were part of the Genesis Genetics records of their studies in this case, and are not disputed by Genesis Genetics, they were omitted from the Defendant, Genesis Genetics' submission to this Court under

the guise, as stated in the footnote at Page 6 of Genesis Genetics' Statement of Undisputed Material Facts, that they were the subject of "hot factual dispute."

22. Plaintiffs, Chaya Grossbaum and her husband, assert that they were never advised by Genesis Genetics and Dr. Hughes or Dr. Licciardi, or anyone else at NYU, that the studies were sub-optimal, that they were disappointing, that risk of ADO was a significant consideration, and that ADO could be responsible for a misdiagnosis and the birth of an affected child if they went ahead with the IVF procedure. (Declaration of Chaya Grossbaum; Pl. Exh. 3.)

23. Attached as Exh. 12 is the *curriculum vitae* of Charles Strom, M.D., Ph.D., FAAP, FACMG, H.C.L.D., Medical Director, Genetic Testing Center Quest Diagnostics, Nicholas Institute (and former Medical Director and Director of the DNA Laboratory at Reproductive Institute in Chicago from May 1988 to October 2000), Plaintiffs' expert.

24. Genesis Genetics and Dr. Hughes provided laboratory services to New York and NYU on approximately 50 occasions. (Hughes Dep. 2/19/09 T:17-13; Pl. Exh. 6.) Genesis Genetics' website lists on a page entitled "Our Partners four fertility clinics in New Jersey including Cooper IVF, New Jersey IVF, RMA New Jersey and South Jersey Fertility. (See copy of website page annexed hereto as Pl. Exh. 13.) In addition, in the Interrogatory Answers at Pages 2 and 3, Genesis Genetics and Dr. Hughes indicated that they were being sued in connection with their laboratory work in the States of California and Tennessee. (Pl. Exh. 14.) Likewise, the resume of his qualifications provided in conjunction with Dr. Hughes' report of March 2, 2010 contains the statement: "Genesis Genetics Institute, where the diagnostic aspects of PGD are provided to over 270 human reproductive centers in North and South America, Europe and now Asia." (Pl. Exh. 15.) Dr. Samuel Pang, Medical Director of the Reproductive Science Center, Lexington, Massachusetts, indicated that "we work with Dr. Hughes for PGD." (Pang Dep. 11/23/10 T:9-18; Pl. Exh. 16.) As far back as July 16, 2004 (the same time that the Grossbaums' studies were being performed), Dr. Hughes was giving a lecture, the abstract of which included his bio in which it was indicated that "last year he formed the Genesis Genetics Institute which performs human embryo testing for couples worldwide." (Pl. Exh. 17.)

25. According to Dr. Hughes, the purpose of soliciting and obtaining the Plaintiffs' agreement to have prenatal testing (CVS or amniocentesis) was not "to facilitate aborting a CF baby," but "to find out the integrity of the single cell testing that we are doing on this project. As a scientist, we have to be monitoring this. If we didn't, it would not be scientific and it certainly would be unethical." Also, Hughes stated, "…we want to monitor the quality of our data, knowing that it isn't perfect. We need to monitor it frequently, and the most frequently we can do it is at a CVS or amniocentesis stage, so that's when we require the testing to be done." And further, "From my personal perspective [Hughes] of this project, that's the only reason…." (Hughes Dep. 2/19/09 T:34-25 to T:37-20; Pl. Exh. 6 in which information was obtained notwithstanding the obstructionism of defense counsel.)

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